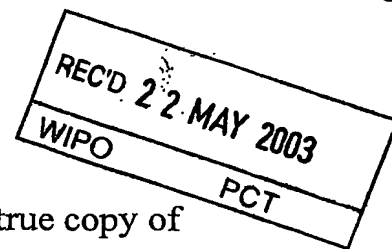


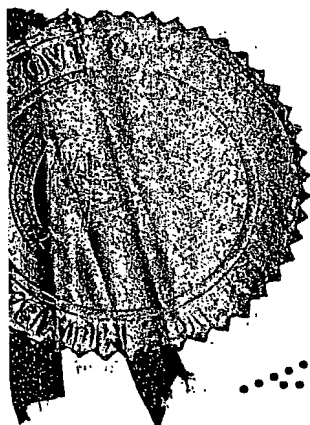
PCT/PTO/18 JAN 2003

PCT / I N 0 3 / 0 0 0 0 6
THE PATENTS ACT, 1970



IT IS HEREBY CERTIFIED THAT, the annex is a true copy of
Application and Provisional specification filed on 10.01.2002 in
respect of Patent Application No. 18/MUM/2002 of Sun
Pharmaceutical Industries Ltd, Acme Plaza, Andheri-Kurla Road,
Andheri(E) Mumbai-400 059, India, an Indian Company.

This certificate is issued under the powers vested on me under
Section 147(1) of the Patents Act, 1970.



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..... Dated this 10th day of February 2003

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ASST CONTROLLER OF PATENTS & DESIGNS



FORM 1

**THE PATENTS ACT, 1970
(39 OF 1970)**

**APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)**

**We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA
ROAD, ANDHERI (E), MUMBAI-400059, INDIA**

AN INDIAN COMPANY

hereby declare -

- (i) that we are in possession of an invention titled "**PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES**"
- (ii) that the provisional specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

**1) Dr. Kilaru Srinivasu 2) Dr. Thennati Rajamannar ; of SUN PHARMA
ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA
390020, GUJARAT, INDIA; an Indian national.**

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

**Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-8397632, FACSIMILE NO- 8212110.**

18/11/2002

10/1/2002

**18 | मुंबई | 2002
MUM**

10 JAN 2002

Handwritten notes and stamps at the bottom right, including a date stamp 10/1/02 and a signature.

Following declaration was given by the inventors-

We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Dated this 9th day of January, 2002.

(Signatures)

1. _____
Dr. Kilaru Srinivasu

2. _____
Dr. Thennati Rajamannar

That to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of a patent to us on this application.

Following are the attachment with the application:

- 1) Provisional specification (3 copies)
- 2) Fee Rs.5000 in cheque bearing No. 186685 dated 9th Jan 2002 on Bank of Baroda.

We request that a patent may be granted to us for the said invention

Dated this 9th day of January, 2002.

X

(Signature) _____

DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LTD.

To

The Controller of Patents,
The Patent Office,
Mumbai - 400 013.

FORM 2

THE PATENTS ACT, 1970
(39 OF 1970)

PROVISIONAL SPECIFICATION
(See section 10)

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

SUN PHARMACEUTICAL INDUSTRIES LTD.

A company incorporated under the laws of India having their office at ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059. MAHARASHTRA, INDIA

The following specification describes the nature of this invention.

18/सुवई/2002
MUM

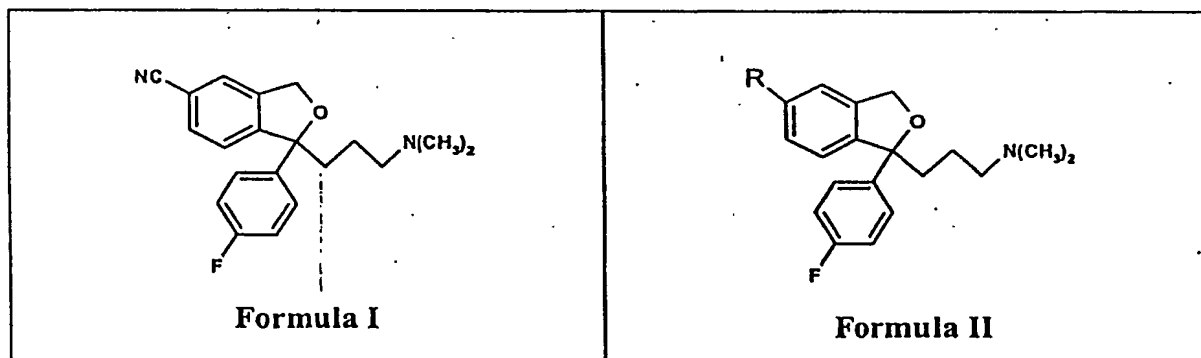
11 0 JAN 2002

PROCESS FOR THE PREPARATION OF 1-[3-(DIMETHYLAMINO) PROPYL]-1-(4-FLUOROPHENYL)-1,3-DIHYDRO-5-ISOBENZOFURAN CARBONITRILE WITH SUBSTANTIALLY LOW LEVELS OF IMPURITIES

The present invention relates to a process for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities. The compound of the process of the present invention 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile (compound of **Formula I**) commonly known as citalopram (INN Name) is a well known antidepressant.

PRIOR ART:

United States Patent No.4,136,193 (hereinafter referred to as '193) claims 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile or its pharmaceutically acceptable acid addition salt. It discloses a process for the preparation of 1-[3-(dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5-substituted derivatives, compounds of **Formula II** wherein R is halogen or trifluoromethyl, by reaction with cyanide source.



The exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile gives the desmethyl citalopram and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

PCT publication WO 0145483 claims a process for producing pure 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile from the penultimate 5- substituted derivatives, compounds of **Formula II**, wherein the R is chloro, bromo, iodo and CF_3 $-(\text{CF}_2)_n$ - SO_2 -O-, n-being 0,1,2,3,4,5,6,7, or 8 by reaction with cyanide source.

The above publication mentions that the exchange process described for the preparation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile found to give the desmethyl 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile and other high molecular weight impurities in unacceptable amounts. Purifying such an impure material makes the process economically unviable.

United Kingdom Patent No. GB 2356199 discloses 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile preparation, which was made using sulfolane as a solvent, instead of dimethylformamide as reported in the '193. Even using sulfolane as a solvent the purity reported by HPLC is about 85%.

A very recent United Kingdom Patent No. GB 2359811 discloses the purification method for 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile wherein the desmethyl citalopram impurity is removed by reacting with an agent which converts it into amide or an amide like neutral derivative, which subsequently can be removed by means of simple operations like acid base treatment. This patent claims use of reagents like acid halides, anhydrides, sulfonyl halides and haloformates and their derivatives to remove the desmethyl citalopram impurity by making amide or an amide like derivative, which transforms basic secondary amine i.e desmethyl citalopram to the neutral form, wherein the tertiary amine viz., the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile remains unaltered, hence displaying the basic character, thereby making the process suitable to eliminate the non basic impurity by means of acid base treatment. However,

this method does not remove the amide impurity, hence the disclosure is not a complete solution to improve the efficiency of the process.

OBJECTIVES OF THE INVENTION

The objective of the current invention is to make 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base in a substantially pure form by removal of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base obtained using cyanide exchange process. When the cyanide exchange reaction was performed, i.e. the conversion of 5-bromo phthalane derivative to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran, it furnished 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with purity ranging between 75-85% by HPLC (area %). As disclosed in the patent literature we found it extremely difficult to remove the impurities and to make the desired quality of pharmaceutically acceptable product.

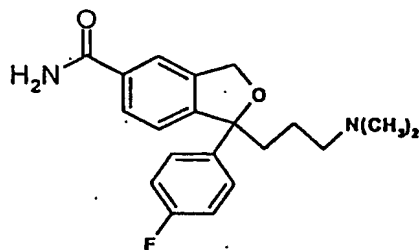
We observed the major impurity that is formed during the course of reaction is the amide impurity viz. 5-carboxamide -1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalide, a compound of **Formula III**, along with desmethyl citalopram impurity viz., desmethyl 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile, a compound of **Formula IV**, herein after these impurities will be referred to as amide and desmethyl citalopram respectively.

Thus for making 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with acceptable purity, it is essential to have an efficient process to avoid the formation of impurities during the cyanide exchange process, or to eliminate the major impurities viz, the amide and desmethyl citalopram by making suitable derivatives. The objective of this invention is conversion of unwanted amide impurity to the desired product viz. to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile along with simultaneous removal of desmethyl citalopram.

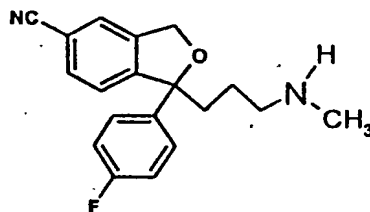
SUMMARY OF THE INVENTION

The present invention provides a process for preparing 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile with substantially low levels of impurities from crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base, the process comprising reacting crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base with an amide reversal agent.

The major impurities that are formed when adopting process disclosed in the '193 patent are compounds of Formulae III and IV and unconverted starting material. Presence of these impurities poses difficulty in purifying the crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base to the desired quality of end product.



Formula III



Formula IV

During the process the amide impurity is formed to an extent of 20%, and normally it ranges from 1 to 20% depending on the reaction conditions. The range of formation of this impurity is so wide, hence developing a process which removes the impurity in one unit operation, say crystallisation or distillation or any other purification, proved to be very difficult and unpredictable. Therefore one needs to use multiple solvent crystallisation to obtain the desired product, which makes the whole process lengthy, and also use of several reactors during purification makes it unworthy.

DETAILED DESCRIPTION OF THE INVENTION:

To devise a suitable process in order to improve purity, we envisaged that reaction of reagents, referred to herein as amide reversal agents, like oxy compounds of phosphorous, acid anhydrides and oxalyl chloride with the crude base would result in the conversion of 5-carboxamide to cyanide i.e. the formation of 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile back from the amide, with concomitant elimination of desmethyl citalopram by forming a neutral species like phosphorous amides.

We found upon treating crude 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile base containing 1-20% of amide and 0.5-10% of desmethyl citalopram with the amide reversal agents of phosphorous oxy compounds, like phosphorous oxyhalides, phosphorous oxides, acid anhydrides, oxalyl chloride etc, preferably with phosphorous oxy compounds, gave substantial enrichment in purity, wherein the amide impurity reduced to below 1% due to reversal of amide to 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran carbonitrile and the desmethyl citalopram to below 1%. With phosphorous oxychloride the amide and desmethyl citalopram impurities reduced to below 0.5%.

The mole ratios of the amide to amide reversal agent are from 0.1 moles to 5 moles with respect to crude citalopram base; the preferred range being 0.1 to 2 mole and the most preferred range being 0.2 to 2 moles. The agents that are employed are phosphorous oxyhalides, phosphorous oxides, acid anhydrides, etc. The halides that one can use are chlorides and bromides, preferred being chlorides. The preferred agents being, phosphorous oxy halides and oxides, wherein phosphorous with valency (III, V), e.g. Phosphorous trichloride (PCl_3), Phosphorous oxychloride (POCl_3), phosphorous pentoxide (P_2O_5), acid anhydrides like acetic anhydride, propionic anhydride, benzoic anhydride and oxalyl chloride. The most preferred reagents being phosphorous oxychloride, and phosphorous pentoxide.

The solvents that are employed for the process are polar to non polar aprotic solvents, ethers like THF, Dioxane, etc, halogen solvents like, dichloroethane, dichloromethane, chlorobenzene, dichlorobenzene etc, hydrocarbons like hexane, cyclohexane, toluene, xylenes etc, esters like methyl acetate, ethyl acetate, benzyl acetate etc, nitriles like acetonitrile, benzonitrile etc and nitro compounds like nitromethane and nitro benzene, the preferred being ethers, aliphatic and aromatic hydrocarbons, aliphatic and aromatic halogen solvents, esters and nitriles and the most preferred being aliphatic and aromatic hydrocarbons, ester and nitrile solvents.

The reaction can be performed at ambient to 200°C, preferably between 50 to 200°C, and most preferably between 50 to 150°C. The reaction time is, between 1 to 20h, preferably between 1 to 15h, most preferably between 1 to 5h.

After the reaction completion, the reaction is discontinued by adding water. The reaction mixture thus obtained is treated with mineral acid like sulphuric or hydrochloric or other mineral acids and organic acids, to adjust the pH 1 to 4, preferably between 1 to 3 and most preferably between 2 to 3 wherein the citalopram is made to form the corresponding acid addition salt, thus making it to solubilise in aqueous medium, the non basic impurities that are formed during reaction with the reagents like phosphorous oxychloride or phosphorous pentoxide to the corresponding phosphorous amide, which can be removed by simple extraction with solvent or most of the times the solvent used for reaction itself suffices to remove the impurity.

Thus the process developed and described provides a viable method of getting high quality and better yield product by reversing the amide impurity to citalopram, and concomitant removal of desmethyl citalopram impurity by forming the neutral derivatives with the amide reversal agents. Hence this process obviates use of multiple solvents and operations making it user friendly.

EXAMPLES

Example 1

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 4.7% amide and 0.72% desmethyl citalopram impurities) and phosphorous oxychloride (POCl_3) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70°C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.05% and 0.23% of amide and desmethyl citalopram respectively.

Example 2

A mixture of 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane(10.0g, 0.03 mol) (containing 5.85% amide and 7.43% desmethyl citalopram impurities) and phosphorous oxychloride (POCl_3) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70°C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.36% and 0.45% of amide and desmethyl citalopram respectively.

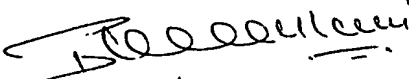
Example 3 :

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane (10.0g, 0.03 mol) (containing 8.27% amide and 0.33% desmethyl citalopram impurities) and phosphorous oxychloride (POCl_3) (2ml, 0.02 mol) in toluene (100ml) was stirred at 70°C under nitrogen atmosphere for 1 hour, poured into water (200ml) and adjusted the pH to 2.0-2.5 with aqueous HCl separated the toluene layer. The pH of the aqueous layer was adjusted to 9.0-9.5 with aqueous ammonia and extracted with toluene (2X100ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.07% and 0.12% of amide and desmethyl citalopram respectively.

Example 4:

A mixture of crude 1-(4'-fluorophenyl)-1-(3-dimethylaminopropyl)-5-cyanophthalane (5.0g, 0.015 mol) (containing 5.8% amide and 1% desmethyl citalopram impurities) and phosphorous pentoxide (P_2O_5) (2.98g, 0.01 mol) in xylene (50ml) was stirred at 140°C under nitrogen atmosphere for 2 hours, poured into water (100ml) and NaOH flakes (5.0g, 0.125 mol) was added to make reaction mixture basic, stirred for 30 minutes separated the xylene layer, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue checked for HPLC purity and found 0.49% and 0.64% of amide and desmethyl citalopram respectively.

Dated this 9th day of January, 2002.

X 
DILIP SHANGHVI
CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED

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